OFFICE OF NAVAL RESEARCH

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TECHNICAL REPORT NO. 119

SHOCK IN THE NONHUMAN PRIMATE

VOLUME II

Abstracts of the Published Literature, 1974-1977

Compiled by

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1 June 1977

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PREFACE

In February 1974, U. S. Navy Technical Report No. 82, "Shock in the Subhuman Primate", was published, covering abstracts of the published literature from 1961-1973. It was felt to be of valuable use to both the basic scientist and clinical investigator. Since the circulation of that publication, we have received numerous requests for an additional volume of abstracts which covers the published literature since that time.

This second volume, "Shock in the Nonhuman Primate", Volume II, has therefore been compiled to summarize the nonhuman primate literature published in the last three years. Also included are a few references prior to 1974 which were overlooked when the first volume was printed. The spectrum of topics has been broadened to include references not directly concerned with shock but very closely related to the shock field.

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B. Rhesus monkey (*Macaca mulatta*)

C. Squirrel monkey (*Saimiri sciureus*)

D. *Macacus cynomolgus*

E. *Macaca cyclopis*

F. Species variation

Dogs *vs* monkeys

Dogs *vs* baboons

I. ENDOTOXIN AND ENDOTOXIC, LIVE E. COLI ORGANISM, OR SEPTIC SHOCK

A. ENDOTOXIN AND ENDOTOXIC SHOCK

MECHANISMS OF BLOOD-VASCULAR REACTIONS OF THE PRIMATE LUNG TO ACUTE ENDOTOXEMIA

Balis, J. U., L. I. Gerber, E. S. Rappaport, and W. E. Neville

Exptl. Mol. Path. 21: 123-137, 1974

Previous studies have related structural and functional changes of the lung in shock to the syndrome of pulmonary leukocytosis (SPL) which is defined as rapid sequestration, degranulation and fragmentation of PMN-leukocytes in the pulmonary vascular bed. In the present study, in vivo and in vitro experiments were performed to investigate the mechanism and significance of ultrastructural changes associated with endotoxin-induced SPL. In rhesus monkeys infused with E. coli endotoxin (5 or 10 mg/kg), sequestered PMN-leukocytes revealed numerous digestive vacuoles containing characteristic membranous particles which were positively identified as particulate endotoxin. In places endotoxin particles were found to be incorporated in the matrix of leukocytic granules as well as in digestive vacuoles released intravascularly from fragmented leukocytes. These changes were associated with progressive degranulation of the PMN-leukocytes as well as multifocal damage to the endothelium of capillaries and arterioles which was demonstrable before the onset of significant leukocytic fragmentation. In addition, formation of digestive vacuoles and degranulation were found to be more prominent in sequestered rather than in circulating PMN-leukocytes. Platelet aggregates and fibrinous deposits in lung capillaries were virtually absent. In vitro endotoxin-leukocyte interaction reproduced all changes seen in sequestered PMN-leukocytes with the exception of leukocyte fragmentation. The results suggest that endotoxin-induced SPL is associated with early development of endothelial damage, and it is largely a manifestation of increased phagocytosis of endotoxin by the marginating PMN leukocytes. The findings also provide strong ultrastructural evidence that phagocytized endotoxin results in direct injury to leukocyte lysosomes, which has not been reported to occur with phagocytosis of inert particles. The above evidence is consistent with previous biochemical data which indicated that endotoxin-induced enzyme release, and potential tissue injury, is greater than that observed with simple phagocytosis.

KEY WORDS: rhesus monkey
endotoxin shock
shock lung
leukocyte damage
platelets
pulmonary leukocytosis, syndrome of
phagocytosis
pulmonary edema
tissue damage

CONTINUOUS ENDOTOXEMIA IN RHESUS MONKEYS AS A CLINICALLY RELEVANT MODEL FOR SHOCK LUNG

Balis, J. U., E. S. Rappaport, L. Gerber, and F. Buddingh

Am. J. Path. 74: 90a, 1974

Seven rhesus monkeys received endotoxin, suspended in Ringer's lactate solution, intravenously via a continuous infusion pump. The duration of the normotensive period could be adjusted by changing the rate of endotoxin infusion. Blood pressure (BP) remained essentially normal throughout a 24-hour period when the rate of endotoxin infusion was 3 mg/kg/hr. With 10 mg/kg/hr, the normotensive period lasted 12 to 15 hours, thereafter the animals developed progressive hypotension which was not reversed by stopping endotoxin infusion. Endotoxin-induced hematologic changes were consistent with disseminated intravascular coagulation (DIC). Morphologic studies demonstrated extensive fibrinous deposits and agglutinated platelets in hepatic sinusoids but not in pulmonary capillaries. Lung changes included interstitial and alveolar edema, generalized swelling and disruption of endothelial and alveolar epithelial cells, and prominent intravascular sequestration and fragmentation of endotoxin-loaded monocytes and degranulated polymorphonuclear leukocytes. Kupffer cells and circulating leukocytes also contained large amounts of endotoxin and they were frequently fragmented.

An additional group of 5 endotoxin-infused monkeys was treated intermittently with methylprednisolone sodium succinate (30 mg/kg every 6 hrs). Steroid treatment was found to inhibit degranulation and fragmentation of the sequestered and circulating leukocytes, DIC and structural lung damage including endothelial disruption and associated edema.

The results indicate that continuous endotoxin infusion is an excellent model to study mechanisms and treatment of pulmonary and other complications of endotoxic shock. In this model glucocorticosteroids were found to inhibit blood-vascular reactions and associated lesions of the lung.

KEY WORDS: rhesus monkey
endotoxin shock
disseminated intravascular coagulation (DIC)
slow infusion of endotoxin
liver pathology
pulmonary edema
steroid treatment

THE RELATIONSHIP OF RETICULOENDOTHELIAL DYSFUNCTION AND ENDOTOXEMIA TO SURVIVAL AFTER HEPATIC ISCHEMIA INJURY IN THE BABOON

Di Luzio, N. R., I. Olcay, K. Holper, T. Drapanas, and R. Trejo

Circ. Shock 2: 77-89, 1975

Among the multiple responsibilties of the liver in homeostasis are the phagocytic activity and detoxifying capacity of the Kupffer cells. By virtue of these qualities the liver has been postulated to play an important role in the maintenance of cardiovascular integrity by removing gut-derived vasoactive substances, bacteria and their endotoxins. The frequent development of gram-negative bacteremia and sepsis after a variety of hepatic insults including hepatic transplantation could be caused, in part, by a depression of the RES with resulting impairment in host-defense mechanisms.

The influence of prolonged hepatic ischemia on the reticuloendothelial system (RES) and hepatocellular function was evaluated in Papio papio baboons to relate alterations in specific cellular functions to subsequent mortality patterns. Alterations in bilirubin, Bromsulphalein, plasma glutamic oxalacetic transaminase, ornithine carbarnyl transferase, lactic dehydrogenase, and alkaline phosphatase did not distinguish the survivors from the nonsurvivor group. Likewise, the degree and persistence of endotoxemia, in the absence of RE dysfunction, did not correlate with the ultimate fate of the animal. In contrast, reticuloendothelial dysfunction, as reflected by the impairment in the clearance of the [^{131}I] triolein RE test lipid emulsion correlated with ultimate mortality pattern. Baboons which developed phagocytic depression at 24 hours posthepatic insult ultimately succumbed, whereas those which manifested minor modifications of RE function survived. In the baboons which ultimately succumbed, endotoxemia always accompanied RE dysfunction. These studies reveal that RE dysfunction may be contributory to fatal outcome in shock causec by hepatic ischemia.

KEY WORDS: baboon
RE system
hepatic ischemia
endotoxin levels in blood
liver function
liver damage

ENDOTOXEMIA IN THE RHESUS MONKEY: ALTERATIONS IN HOST LIPID AND CARBOHYDRATE METABOLISM

Fiser, R. H., J. C. Denniston, and W. R. Beisel

Ped. Res. 8: 13-17, 1974

Experimentally induced endotoxemia in the rhesus monkey produced a two- to four-fold increase in plasma triglyceride concentration; glucose administration partially prevented this rise. Plasma free fatty acid and phospholipid values were depressed 40-50% of control values whereas cholesterol values were unchanged. Endotoxin-treated monkeys displayed showed glucose disappearance (K values, 2.2 vs. 1.1) and higher levels of sugar in blood when given glucose (72±8 mg/100 ml vs. 151±11 mg/100 ml). These studies indicate that endotoxin has a marked effect on the pattern of substrate utilization by the host.

The present data document important alterations in carbohydrate and lipid metabolism during endotoxemia. Hyperglycemia was evident within 2 hr and slowed utilization of glucose was observed in endotoxic monkeys given glucose. A similar tendency to hyperglycemia has been reported due to Escherichia coli sepsis in baboons. An absolute or relative insulin lack, possibly related to catecholamine excess, has been suggested to explain these findings. Insulin resistance due either to free fatty acid increases or increased secretion of pancreatic glucagon could also contribute to the elevated glucose concentrations. In contrast to these results, a significant hypoglycemia during gram sepsis has been described in neonates and increased glucose utilization has been postulated as a possible cause.

KEY WORDS: rhesus monkey, endotoxin, WBC count, fever, carbohydrate metabolism, lipid metabolism, glucose, insulin

EFFECTS OF GRAM NEGATIVE ENDOTOXEMIA ON MYOCARDIAL CONTRACTILITY IN THE AWAKE PRIMATE

Geocaris, T. V., E. Quebbeman, R. Dewoskin, and G. S. Moss

Ann. Surg. 178: 715-720, 1973

Findings concerning changes in myocardial contractility during endotoxemia remain controversial. The authors' objective was to study the effects of endotoxemia on myocardial contractility in the awake, intact primate.

Six adult baboons (Papio doguera) weighing 12.8 to 18.2 kg were test animals. Siliconized, heparin-saline filled polyetheylene catheters (PE-350) were surgically implanted into the left ventricle through a puncture in the apical dimple. On the day prior to study, siliconized polyethylene catheters (PE-240) were placed into the aortic arch and superior or inferior vena cava via axillary or femoral cutdowns under light phencyclidine tranquilizer, 0.6 mg/kg. The ventricular catheter was exposed and the animal placed in a specially designed restraining chair and given an intravenous drip of 5% dextrose in 0.9 normal saline overnight. A Statham SF-1 catheter tip transducer was passed through the chronically implanted ventricular catheter into the ventricular chamber. Cardiac outputs were determined with indocyanine green dye dilution techniques using a Beckman Cardiodensitometer.

The study was divided into three periods: baseline, 2 hr of endotoxemia, and 4 hr of endotoxemia. Endotoxemia was induced by infusing a 4.55 mg/kg bolus dose of endotoxin (E. coli, 026:B6, Difco) in 30 cc normal saline intravenously over a 10-min period. This was followed by a constant infusion of endotoxin at 1 mg/kg/hr to maintain a relatively constant level of endotoxemia.

The early phases of endotoxemia are characterized by tachycardia, hypotension and development of a base deficit. There were no significant changes in cardiac output or myocardial contractility in the early stages of endotoxemia when increased sympathetic activity was evident.

Although the contractility data expressing the relationship of dP/dt to developed pressures showed no statistically significant changes during endotoxemia, a transient initial increase in 4 of the 6 animals was followed by a depression in contractility in the same number of animals. An early increase in contractility should be expected as a result of catecholamine release induced by endotoxin.

It appears that myocardial contractility is maintained or enhanced in the early states of endotoxemia when increased sympathetic activity is present. However, myocardial depression may be seen in the later stages of endotoxemia once the protective effects of the endogenous catecholamines are exhausted. These late changes in myocardial contractility seen in the isolated dog heart preparation should be searched for in the intact, awake primate.

KEY WORDS: baboon
endotoxin shock
myocardial performance
heart function
heart failure
instrumented ventricle
cardiac output (dye)

CARDIOPULMONARY EFFECTS OF VOLUME LOADING OF PRIMATES IN ENDOTOXIN SHOCK

Greenfield, L. J., R. H. Jackson, R. C. Elkins,
J. J. Coalson, and L. B. Hinshaw

Surgery 76: 560-572, 1974

The present study was designed to evaluate primate myocardial performance in endotoxin shock and the cardiopulmonary response to fluid loading with colloid. Also tested was the validity of using PAW pressure to assess left ventricular filling pressure as opposed to direct catheterization of the left ventricle to measure LVEDP.

Myocardial performance was evaluated in rhesus monkeys after endotoxin shock, and the responses to fluid loading with colloid were measured in both anesthetized control and experimental groups. Minute work and cardiac output (CO) were decreased in 5 monkeys after 6 hours endotoxin to levels significantly below control values. Infusing colloid to a mean left ventricular end diastolic pressure (LVEDP) of 12 to 15 mmHg increased both CO and minute work significantly but they remained one half that of the control group of 4 primates after fluid loading. Improved cardiac performance persisted after infusion through a 30-minute recovery stage when LVEDP returned to normal. Simultaneous pulmonary arterial wedge pressure (PAW) pressures showed some correlation with LVEDP reading up to 6 mmHg, but above that level the PAW underestimated the LVEDP by 3 to 6 mmHg. Microscopic study showed that fluid loading produced comparable pulmonary edema in both groups, but endotoxin produced ultrastructural capillary lesions. A normal PAW pressure after fluid administration can occur after transient overloading of the left ventricle. Since interstitial pulmonary edema is not readily reversible, persistent respiratory insufficiency may result and the cause be unsuspected unless ventricular filling pressures are monitored during fluid administration.

KEY WORDS: rhesus monkey
endotoxin shock
fluid administration
cardiac function
cardiac dysfunction
pulmonary artery wedge pressure
left ventricular end diastolic pressure
cardiac output

THE RELATIONSHIP OF CIRCULATING ENDOGENOUS ENDOTOXIN TO HEMORRHAGIC SHOCK IN THE BABOON

Herman, C. M., et al.

Ann. Surg. 179: 910-916, 1974

See Section on Hemorrhagic Shock, page 33.

ULTRASTRUCTURAL CHANGES IN THE LIVER OF BABOONS FOLLOWING LEAD AND ENDOTOXIN ADMINISTRATION

Hoffmann, E. O., N. R. Di Luzio, K. Holper,
L. Brettschneider, and J. Coover

Lab. Invest. 30: 311-319, 1974

Adult baboons received intravenous injections of either lead acetate or endotoxin, or both substances combined. The administration of lead or endotoxin alone did not induce any mortality, but simultaneous injection of both substances resulted in a 100% mortality rate. Ultrastructural changes in the group which received lead were characterized by vacuolization of some Kupffer cells and the presence of finely granular electron-dense material. A very small number of parenchymal cells manifested degenerative changes. The endotoxin group presented few fibrin deposits in the sinusoids and degenerative changes in a small proportion of both Kupffer and parenchymal cells. The morphologic alterations produced by the combination of lead and endotoxin were marked and consisted of large deposits of fibrin and the presence of cellular debris and inflammatory cells in the sinsuoids. Vacuolization and autophagocytosis of Kupffer and parenchymal cells as well as necrosis and formation of large multivesicular bodies and fat droplets occurred in parenchymal cells. The space of Disse was frequently obliterated by protein deposits. A finely granular electron-dense material was also observed within liver cells and the sinusoids. Incipient lead inclusion bodies were present in the nucleus of Kupffer and parenchymal cells.

The present experiment demonstrates that a single injection of lead acetate or endotoxin alone induces ultrastructural changes in a limited number of Kupffer and parenchymal cells and that the combination of these two substances has a synergistic lethal effect associated with prominent degenerative changes in the liver. In view of increasing concern for environmental contamination by heavy metals and the increasing clinical incidence of endotoxemias, the possibility exists of the occurrence of similar synergistic pathologic effects in man. Although there is no presently known clinical state referable to lead-endotoxin interaction and since our experimental conditions were not undertaken to simulate any known circumstance of lead exposure in man, further experiments will be required to elucidate the probability of occurrence of a synergistic effect of lead-endotoxin interaction in man.

KEY WORDS: baboon
endotoxin
lead-endotoxin interactions
liver ultrastructure

LYSOSOMAL DISRUPTION DURING THE DEVELOPMENT OF ENDOTOXIC SHOCK IN THE BABOON

Jansön, P. M. C., S. H. Kühn, and J. J. Geldenhuys

S. Afr. Med. J. 49: 1041-1047, 1975

Lysosomal disruption with release of lysosomal enzymes has been described in shock. Our study was designed to demonstrate the release of lysosomal enzymes in the liver and lung in addition to determining circulating serum lysosomal enzyme values.

Therapeutic means of reducing or inhibiting lysosomal disruption were also investigated. Five groups of baboons were investigated:

Group A: (control group)--no endotoxin or treatment administered.

Group B: (endotoxin only)--liver and lung tissues showed an increase in free lysosomal enzymes, and a similar increase in circulating serum lysosomal enzymes was demontrated.

Group C: (chloroquine treatment [lysosomal stabiliser] following endotoxin administration)--the liver and lung tissues showed a smaller increase in free lysosomal enzymes and a corresponding lesser increase in circulating serum lysosomal enzymes was demonstrated.

Group D: (dexamethasone treatment [lysosomal membrane stabiliser] following endotoxin administration)--the rise in lysosomal tissue and serum enzyme values was less than that in Group B.

Group E: (combination of chloroquine and dexamethasone treatment following endotoxin administration)--the rise in lysosomal tissue and serum values was less than that demonstrated in Group B.

The survival of the animals in the various groups correlated well with the lysosomal enzyme tissue and serum values, as did the monitored hemodynamic, hematological and other parameters.

These findings indicate that an experimental basis has been established for the administration of corticosteroids in shock. Chloroquine has been shown experimentally to have a lysosomal stabilising effect, and in combination with dexamethasone it had an even greater stabilising effect. Obviously, the early administration of chloroquine and steroids is of prime importance, as they are of little value once lysosomal disruption has taken place. Results indicate that lysosomal disruption, with consequent enzymatic release, takes place well before the typical disturbances in hemodynamic criteria are observed. In the clinical situation, endotoxic shock frequently develops with devastating rapidity, with little indication of the impending catastrophe being evident in the usually monitored hemodynamic parameters. Our studies would suggest that a sequential serum assay for circulating acid phosphatase and β-glucuronidase might be used as a parameter in conjunction with monitoring of coagulation

changes, to detect the early phase of endotoxicosis and to indicate effectiveness or ineffectiveness of treatment.

These experiments also demonstrate an increase in free and particulate lysosomal enzyme activity in lung fractions, thus emphasizing the crucial role played by the lungs in the syndrome of shock, as has been mentioned by other investigators.

The suppression of lysosomal enzyme activity modified the course of endotoxic shock in these experiments, and resulted in the survival of 10 of the 15 treated baboons.

KEY WORDS: baboon
endotoxin shock
lysosomal disruption
liver function
steroid treatment

ERYTHROCYTE 2,3-DIPHOSPHOGLYCERATE IN ENDOTOXIC SHOCK IN THE SUBHUMAN PRIMATE: RESPONSE TO FLUID AND/OR METHYLPREDNISOLONE SUCCINATE

Johnson, G., Jr., N. B. McDevitt, and H. J. Proctor

Ann. Surg. 180: 783-786, 1974

The effects of shock as a result of Escherichia coli endotoxin on certain hemodynamic and biochemical parameters and mortality were studied in the baboon.

Twenty-four healthy baboons (Papio doguera) weighing 13-27 kg were sedated with Sernylan (phencyclidine hydrochloride, 1 mg/kg), given intramuscularly, and secured in an upright position in a primate restraining chair. Animals were given 30 min to recover from Sernylan prior to the experiment. No additional anesthesia was administered. Cardiac output was determined at each sampling time by the dye dilution method using indocyanine green and a Beckman cardiodensitometer. Red blood cell 2,3-DPG was determined using a modification of the microfluorometric method of Keitt (J. Lab. Clin. Med. 77: 470, 1971). Arterial lactate was measured using the modification of the enzyme analysis method described by Bergmeyer (Methods of Enzymatic Analysis; New York, Academic Press, 1963).

The ability of methylprednisolone succinate (MSP) in massive doses and/or rapid infusion of a buffered electrolyte solution to influence the results was then examined. Shock secondary to Escherichia coli endotoxin was associated with a decrease in RBC 2,3-DPG. This fall in RBC 2,3-DPG was not significantly influenced by MPS. Likewise, MPS did not prevent the changes in oxygen metabolism or systemic hemodynamics, nor was it associated with any decrease in mortality associated with endotoxic shock. Buffered electrolyte solution therapy improved both hemodynamics and mortality, but did not significantly protect against changes in RBC 2,3-DPG.

KEY WORDS: baboon
endotoxin shock
2,3-DPG
cardiac output (dye)
methylprednisolone

FEVER PRODUCED IN THE SQUIRREL MONKEY BY INTRAVENOUS AND INTRACEREBRAL ENDOTOXIN

Lipton, J. M., and D. E. Fossler

Am. J. Physiol. 226: 1022-1027, 1974

Are the subhuman primates suitable models for fever research? The available data on the Rhesus macaque, the baboon, and the chimpanzee suggest that these primates fail to respond, or respond minimally or inconsistently, to systemic administration of bacterial endotoxins that cause fever in man. The main aim in the present experiments was to develop a primate model that consistently responds to endotoxin challenge with reliable and quantitative febrile responses and that also has a large, well-differentiated brain suitable for precise research on the central mechanisms of fever.

Male squirrel monkeys weighing 400-600 g were used. The monkeys were kept in individual cages in a neutral thermal environment (21-25°C) and were tested in an environmental chamber controlled at 23±0.5°C. Before surgery and testing, each monkey was trained to sit quietly in a restraining chair especially designed for the species. The first experiments were performed on animals with indwelling cannulas 18 days after the surgey. The animals were weighed and placed in a restraining chair inside the environmental chamber. Rectal temperature and three skin temperatures (thigh, plantar portion of the foot, and base of the tail) were measured, using thermistor probes held in position with Velcro tape. The temperature at each site was recorded every 5 min using a Digitec temperature recording system. After a baseline period of 1 hr or more, the injections were made.

Rectal temperature (T_r) was recorded for 5 hr after S. typhosa endotoxin was injected into the saphenous vein or into intracerebral sites in squirrel monkeys resting in a 23°C environment. Intravenous injections (0.08-100 µg/kg) produced monophasic febrile responses with maximum temperature increments that were related to the amount of endotoxin administered. Intracerebral injections of 500 ng endotoxin in 1 µl of saline caused high or maximal fevers of long duration when placed in some sites in the diencephalon and little or no febrile response when injected into other sites. Injecting sodium pentobarbital into endotoxin-sensitive brain sites caused slowly developing increases in T_r. Prostaglandin E_1 (PGE_1, 500-750 ng) placed into similar sites caused rapid and brief febrile responses while an equal amount of dibutyryl-cyclic-AMP had no effect on T_r. The susceptibility of the squirrel monkey to peripheral and central administration of an endotoxin that causes fever in man, together with previous reports which show that other primates respond minimally or not at all to peripheral pyrogens, suggests that this species is an especially appropriate primate model for fever research. The results on intracerebral injections further suggest: 1) that central endotoxin may produce fever by depressing neuronal activity, and 2) that febrile states observed after central injections of PGE may not depend on an acceleration of cyclic AMP activity in local brain cells.

KEY WORDS: squirrel monkey; endotoxin (intravenous vs. intracerebral); prostaglandin E_1; fever; CNS; regional temperatures

FEVER PRODUCED BY ENDOTOXIN INJECTED INTO THE HYPOTHALAMUS OF THE MONKEY AND ITS ANTAGONISM BY SALICYLATE

Myers, R. D., T. A. Rudy, and T. L. Yaksh

J. Physiol. 243: 167-193, 1974

A bacterial pyrogen injected intravenously produces a fever which is characterized by two distinct peaks. Although both of these peaks may be mediated by endogenous pyrogen, it has been suggested that the first peak is caused by a direct action of the injected endotoxin on the central nervous system. The second peak of this biphasic response is thought to be caused by an action upon the hypothalamic thermoregulatory centres of an endogenous pyrogen released from granulocytes in the blood, which are "activated" by coming in contact with the injected endotoxin.

The present experiments were carried out to determine the anatomical regions in the brain stem which are sensitive to endotoxin. Since a salicylate may exert its antipyretic effect by preventing a blood-borne pyrogen from passing into the brain, the effect of sodium salicylate on a fever produced by an endotoxin administered centrally was examined further.

A suspension of the killed cell bodies of either E. coli, S. dysenteriae or S. typhosa was microinjected through cannulae implanted chronically at specific sites within the diencephalon and mid-brain of the unanesthetized monkey. A biphasic, monophasic or an undifferentiated fever could be induced by each type of microorganism, but the type of response depended solely upon the locus of injection.

Although little difference in the potency of the three pyrogens was found, the rise in body temperature was in each instance dependent upon the concentration of the endotoxin. A more intense fever was accompanied by shivering, vasoconstriction of the ear vessels, piloerection and huddling behaviour. Tolerance to the pyrexic effect of repeated injections of endotoxin did not develop.

The febrile response having the shortest latency, greatest maximum rise in temperature and largest 10-hr fever index was evoked by microinjections into the anterior hypothalamic, preoptic area. The incidence of biphasic fevers was also greater after endotoxin was injected into this same region. Endotoxin given similarly in the posterior hypothalamus or in the mesencephalon had either no effect or produced a smaller elevation in temperature after a longer latency. The distance of an injection site from the coronal plane formed by the optic chiasm and anterior commissure correlated significantly with the latency and magnitude of the temperature change as well as the fever index.

When given intravenously, endotoxin in a quantity at least 100 times greater was required to evoke a fever similar to that produced when the pyrogen was microinjected into the anterior hypothalamic preoptic region. However, a biphasic fever was evoked with a latency of from 3-15 min when a larger amount of endotoxin was injected intravenously. Tolerance developed rapidly to the febrile effect of endotoxin administered by this route although toxic reactions were not observed.

After the fever evoked by the hypothalamic injection of endotoxin had reached a plateau, 300-1200 mg sodium salicylate administered intragastrically produced a dose-dependent fall in temperature, but had no effect on the body temperature of an afebrile monkey.

It is concluded that in the rhesus monkey, a bacterial pyrogen can evoke a fever which is mediated entirely by an action on the central nervous system, the principal site being the anterior hypothalamic, preoptic area. The first phase of a biphasic fever caused by bacteria acting either by the central or peripheral route seems to be due either to a direct action of the pyrogen on the cells of the anterior hypothalamus, or to the secondary release within this region of an intermediary thermogenic substance such as 5-hydroxytryptamine or prostaglandin. The finding that sodium salicylate counteracts a centrally evoked fever is not compatible with the hypothesis that an antipyretic exerts its action by preventing a pyrogen that is circulating in the blood stream from entering the central nervous system.

KEY WORDS: rhesus monkey
endotoxin
pyrogens
hypothalamus
fever
salicylate

EFFECTS OF STEROID PRETREATMENT ON DEVELOPMENT OF SHOCK LUNG: HEMODYNAMIC, RESPIRATORY AND MORPHOLOGIC STUDIES

Pingleton, W. W., J. J. Coalson, L. B. Hinshaw, and C. A. Guenter

Lab. Invest. 27: 445-456, 1972

The pathogenesis of the pulmonary injury in shock is obscure. Recent studies have emphasized pulmonary vascular changes, including the presence of dilated pulmonary capillaries filled with leukocytes which degranulate and disintegrate. This study explores the possibility that release of leukocyte lysosomes in the pulmonary capillaries might cause endothelial damage, and that these effects could be obviated by the stabilization of leukocyte lysosomes with steroid or salicylates.

Rhesus monkeys subjected to endotoxin shock were pretreated with low dose corticosteroids (cortisone acetate 15 mg/kg), high dose corticosteroids (methylprednisolone 30 mg/kg), or salicylates (sodium salicylate 100 to 400 mg/kg) and compared with a nonpretreated control group in endotoxin shock. Cardiac output, systemic arterial pressure, minute ventilation, oxygen consumption, physiologic dead space, and the alveolarterial oxygen gradient were similar in the two groups during the 120-min study. Light and electron microscopic studies of lung sections demonstrated polymorphonuclear leukocyte sequestration, degranulation, and fragmentation in the pulmonary capillaries. Additional findings included endothelial abnormalties with focal areas of alveolar and perivascular space edema. These findings were similar in pretreated and nonpretreated groups.

Twelve monkeys subjected to hemorrhagic shock were studied with or without pretreatment with 30 mg/kg of methylprednisolone. No signifidant hemodynamic, respiratory or histologic differences were apparent between the two groups.

Pretreatment of endotoxin shock with steroids or salicylates, or hemorrhagic shock with steroids, did not significantly improve the hemodynamic effects of shock. Furthermore, the antiinflammatory substances did not prevent leukocyte sequestration in the pulmonary capillaries or other histologic abnormalities characteristically seen in the lungs in the early phase of shock.

KEY WORDS: E. coli endotoxin shock
hemorrhagic shock
pulmonary ultrastructure
pulmonary function
steroid pretreatment
therapy
rhesus monkey
shock lung
cardiovascular function
lysosome
leukocyte

SIGNIFICANCE OF LEUKOCYTES IN ENDOTOXIC SHOCK

Pingleton, W. W., J. J. Coalson, and C. A. Guenter

Exptl. Mol. Path. 22: 183-194, 1975

Peripheral blood leukopenia and the sequestration of large numbers of polymorphonuclear leukocytes in pulmonary capillaires have been observed in experimental shock. It has been suggested that the lysosomal enzymes released from these damaged and sequestered leukocytes may contribute to systemic hypotension and pulmonary capillary damage. This study was undertaken to evaluate the role of leukocytes in endotoxic shock.

Six rhesus monkeys rendered leukopenic by total body irradiation (mean white blood count, 358/cu mm) were compared with six normal nonleukopenic monkeys (mean white blood count, 10,550/cu mm) for 2 hours after injection of E. coli endotoxin. The effects of irradiation alone were evaluated in three additional animals which did not receive endotoxin.

Following the injection of endotoxin, the mean cardiac output and systemic pressure decreased more than 50% in both the leukopenic and normal groups. Metabolic acidosis developed in both groups. The mean arterial PO_2 was unchanged, but the alveolar-arterial O_2 gradients increased. Differences between the two injected groups were not significant in these parameters.

Light and electron microscopy demonstrated sequestered polymorphonuclear leukocytes and platelets in pulmonary capillaries in the nonirradiated group, but leukocytes were virtually absent in sections from lungs of the leukopenic animals. In spite of this difference, significant endothelial swelling and perivascular edema were demonstrable in both groups. No significant histologic abnormalities were noted in the three irradiated leukopenic control animals who did not receive endotoxin.

Leukopenia provided no protection from the hemodynamic effects or the histological damage in pulmonary capillaires observed after administration of endotoxin.

KEY WORDS: rhesus monkey
WBC, role of
leukopenia
pulmonary leukocytosis
shock lung
endotoxin shock
artificial production of leukocytosis
pulmonary damage
pulmonary ultrastructural changes

ENDOTOXIC SHOCK IN THE BABOON: THE EFFECTS OF GLUCOCORTICOID THERAPY

Rao, P. S., and D. Cavanagh

Surg. Forum 11: 416-419, 1970

The present study was undertaken to evaluate the effect of methylprednisolone sodium succinate (Solumedrol) in experimental endotoxic shock. Baboons were sedated using phencyclidine hydrochloride (Sernylan) intramuscularly in a dose of 2 mg/kg of body weight and intravenous pentobarbital sodium was used as required for anesthesia. Cardiac output and mean transit time were estimated by the dye-dilution method of Hamilton and Stewart, utilizing indocyanine green. Plasma volume was obtained by the dilution method of Gregerson and Rawson, utilizing Evans blue.

Baboons were divided arbitrarily into four groups: Group A consisted of 10 baboons given lipopolysaccharide Escherichia coli (0127:B8) 7 mg/kg of body weight intravenously. Group B was composed of 10 baboons which received coliform endotoxin and subsequently were treated with intravenous administration of Solumedrol 15 mg/kg of body weight. Group C consisted of 2 baboons observed for the effects of experimental technique alone, without administration of lipopolysaccharide Escherichia coli. Group D consisted of 4 baboons which received a similar sham operation without endotoxin, but with Solumedrol being given intravenously in a dose of 15 mg/kg of body weight.

The hemodynamic changes in endotoxic shock showed some improvement following the administration of Solumedrol in pharmacologic doses. Although Solumedrol did not appear to maintain the renal artery flow in the initial stages, the fall was relatively less pronounced in the late phase of endotoxic shock. The aortic pressure fell progressively but this fall too was less pronounced. The 33% reduction in cardiac output with corticosteroid therapy compares favorably with a mean fall of 52% when no supportive therapy was given. Corticosteroids maintained the plasma volume remarkably well. In contrast to baboons receiving endotoxin alone, in which the peripheral resistance was markedly elevated, the corticosteroid treated baboons showed a reduction in peripheral resistance at 60 minutes, suggestive of vasodilatation. A rise in the blood lactic level was a consistent finding whether the baboons received the steroid or not. This study suggests that corticosteroids in pharmacologic doses appear to reduce the deleterious effects of coliform endotoxin in the subhuman primate and suggests some of the more obvious mechanisms by which this may occur.

KEY WORDS: baboon
endotoxin shock
steroid therapy
plasma volume (dye)
cardiac output (dye)
lactic acid

CARDIOVASCULAR AND METABOLIC EFFECTS OF WHOLE OR FRACTIONATED GRAM-NEGATIVE BACTERIAL ENDOTOXIN IN THE UNANESTHETIZED RHESUS MONKEY

Reichgott, M. J., K. L. Melmon, R. P. Forsyth, and D. Greineder

Circ. Res. 33: 346-352, 1973

Rhesus monkeys were infused with endotoxin lipopolysaccharide (LPS) (10 mg/kg [LPS_{10}] or 2.5 mg/kg [$LPS_{2.5}$]) or with fractions of LPS containing 6.3% lipid (PS_1) or 0.5% lipid (PS_2) (2.5 mg/kg). Systemic and regional hemodynamics, leukocyte counts, blood gases, pH, and plasma bradykinin concentration were measured. Monkeys receiving LPS_{10}, $LPS_{2.5}$, or PS_1 became hypotensive (mean blood pressure -37±10 mmHg) and had decreased peripheral vascular resistance (-10% to -24% of the base line), compensated metabolic acidosis, and elevated plasma bradykinin concentrations (14±6 ng/ml) 2 hrs after infusion. Vasodilation occurred in coronary, hepatic, and splanchnic vasculature; vasoconstriction occurred in the spleen. Cardiac output was diverted from muscle to viscera. Monkeys receiving PS_2 were normotensive with elevated peripheral vascular resistance (+46%) and no measurable plasma bradykinin concentration. By 6 hours, marked elevation of peripheral vascular resistance developed in monkeys given LPS_{10} (+113%) and $LPS_{2.5}$ (+57%). Monkeys receiving PS_1 returned to baseline values, but monkeys receiving PS_2 remained unchanged. Leukopenia (-50% to -65%) was persistent only in monkeys receiving LPS or PS_1. Toxicity of LPS apparently depends on the lipid portions of the molecule. Vasodilation and bradykinin generation are correlated with persistent granulocytopenia. Late toxicity may be independent of early cardiovascular events.

KEY WORDS: rhesus monkey
endotoxin
bradykinin
cardiac output
granulocytopenia
lipopolysaccharide
microspheres
polysaccharides
regional blood flow

COMPARISON OF HEMODYNAMIC AND REGIONAL BLOOD FLOW CHANGES AT EQUIVALENT STAGES OF ENDOTOXIN AND HEMORRHAGIC SHOCK

Rutherford, R. B., J. V. Balis, R. S. Trow, and G. M. Graves

J. Trauma 16: 886-897, 1976

Hemodynamic, respiratory, and regional blood flow measurements were carried out in two groups of monkeys at three roughly equivalent stages of endotoxin and hemorrhagic shock. Comparisons revealed characteristic differences at the two early stages, particularly in systemic vascular resistance and the pattern of distribution of cardiac output. However, at the final stage of shock, these patterns had merged and there were no characteristic differences between the two groups. The pathologic significance of these findings, in terms of the endotoxin theory of irreversible hemorrhagic shock and the relative contributions of vasoactive humoral substances at various stages of the two forms of shock, is discussed.

KEY WORDS: rhesus monkey
endotoxin shock
hemorrhagic shock
hemodynamic changes
regional blood flow

GLUCOCORTICOID EFFECT ON HEPATIC CARBOHYDRATE METABOLISM IN THE ENDOTOXIN-SHOCKED MONKEY

Schuler, J. J., P. R. Erve, and W. Schumer

Ann. Surg. 183: 345-354, 1976

The ability of glucocorticoids to protect animals from the lethal effects of endotoxemia was first demonstrated over 40 years ago. Nevertheless, this protective effect of glucocorticoids has not been sufficiently defined in the endotoxified subhuman primate. This study was, therefore, designed to answer the following questions: Do pharmacologic doses of glucocorticoids protect the subhuman primate from lethal endotoxemia as effectively as they do lower animals? Do the same endotoxin-induced derangements in carbohydrate metabolism and energy production that occur in lower animals also occur in the subhuman primate? If so, can these derangements be obviated by the administration of glucocorticoids? Is there a relationship between abnormal carbohydrate metabolism and the ability to maintain a normal hepatic level of high-energy nucleotide phosphates in the endotoxin-shocked primate?

This study investigated the effect of glucocorticoid treatment on survival, on hepatic carbohydrate metabolism, and on levels of hepatic adenine nucleotides in the endotoxin-shocked monkey. Dexamethasone sodium phosphate (DMP) administered either at the time of endotoxin challenge or up to 90 minutes afterward significantly increased the survival rates. Endotoxin administered alone caused profound hypoglycemia and lactic-acidemia, which were alleviated by the administration of DMP. Endotoxin administered alone significantly decreased the hepatic levels of glucose-6-phosphate, fructose-6-phosphate, phosphoenolpyruvate, adenosine triphosphate, adenosine diphosphate, and glycogen; and it significantly increased the hepatic levels of fructose-1,6-diphosphate, lactate, and adenosine monophosphate. The administration of DMP at the time of endotoxin challenge maintained the levels of all these metabolites at or near the control levels.

KEY WORDS: cynomolgus monkey
endotoxin shock
liver
steroid therapy
glucose
hypoglycemia

B. LIVE *E. COLI* ORGANISM SHOCK OR SEPTIC SHOCK

ESCHERICHIA COLI BACTEREMIC SHOCK IN CONSCIOUS BABOONS

Buckberg, G., J. Cohn, and C. Darling

Ann. Surg. 173: 122-130, 1971

Since the subhuman primate is phylogenetically more related to the human than is the dog, it may be a more suitable experimental animal for the study of bacteremic shock as it occurs in man. To eliminate objections relating to the use of dogs, general anesthesia, and endotoxin, the present study was performed in conscious subhuman primates (baboons) given live E. coli organisms. The purposes of the study were: (1) to observe hemodynamic and metabolic effects of bacteremic shock in baboons, (2) evaluate the reproducibility and limitations of the method, (3) determine if the observed changes parallel responses reported in man.

The effects of gram negative bacteremic shock (E. coli) were studied in unanesthetized baboons. Twelve animals received E. coli, while five were controls. Two phases of hemodynamic response were observed. During the first two hours, shock was characterized by tachycardia, maintenance of normal cardiac output and decreased peripheral vascular and pulmonary vascular pressure and resistance. In the second phase (3 hours) tachycardia persisted, peripheral resistance and pulmonary resistance returned to control values, sytemic arterial pressure increased slightly, and cardiac output declined. Hypoxia and lactic acidosis occurred in animals undergoing septic shock. All septic animals died within 24 hrs after study. While this study was limited by the difficulties in standardization of E. coli dosage, it suggests that the conscious subhuman primate (baboon) is an appropriate model from which results of experimental septic shock may be extrapolated to man.

KEY WORDS: baboon
E. coli shock
unanesthetized animals
live E. coli organisms
lactic acid

PATHOPHYSIOLOGIC RESPONSES OF THE SUBHUMAN PRIMATE IN EXPERIMENTAL SEPTIC SHOCK

Coalson, J. J., L. B. Hinshaw, C. A. Guenter, E. L. Berrell, and L. J. Greenfield

Lab. Invest. 32: 561-569, 1975

The grave clinical aspects of septic shock have stimulated the search for an experimental animal model which more closely relates to human pathophysiology. This study of the cardiovascular-pulmonary-morphologic responses of the baboon to slow infusions of live Escherichia coli organisms was designed to approximate more closely the human clinical entity. Anesthetized young adult baboons received 3-hour intravenous infusions of organisms at an average dosage of 8×10^9 organisms per kg. body weight. Responses of animals were followed during a period of 6 hours in the anesthetized state. There was progressive systemic hypotension and steadily decreasing cardiac output. Total peripheral resistance was uniformly depressed during the infusion, but was variable during the post-infusion survival period. Increases in heart rate, alveolar-arterial oxygen tension gradient, and oxygen uptake were uniformly present. These alterations bear close resemblance to those seen in other subhuman primates administered short term doses of live organisms. There were extensive morphologic changes in pulmonary, cardiac, and renal beds. Glomeruli contained multiple fibrin thrombi and disrupted platelets, and the glomerular capillary endothelium was focally edematous and disrupted. The myocardium exhibited capillary endothelial edema and fluid accumulation in interfiber and intrafiber spaces. There were sequestration, degranulation, and fragmentation of polymorphonuclear leukocytes and platelets, and characteristic endothelial lesions within the pulmonary vascular bed. Findings demonstrate both cardiovascular-pulmonary dysfunction and renal, cardiac, and pulmonary morphologic lesions. The baboon shock model appears to be well suited for studies of experimental septic shock and bears close resemblance to the human clinical entity.

KEY WORDS:
baboon
endotoxin shock
septic shock
live E. coli organisms
hemodynamics in shock
fibrin thrombi
heart dysfunction
renal function
intravascular coagulation
pulmonary dysfunction

THE EFFECT OF ADRENOCORTICOSTEROID PRETREATMENT ON KININ SYSTEM AND COAGULATION RESPONSE TO SEPTIC SHOCK IN THE BABOON

Herman, C. M., G. Oshima, and E. G. Erdös

J. Lab. Clin. Med. 84: 731-739, 1974

The Hageman factor may perform a central role in shock because it can activate the kallikrein-kinin, intravascular coagulation, and serum complement systems. Activation of these systems can then result in generalized vascular damage, interference with tissue perfusion, hypotension, and consequent cellular and organ impairment. Therefore, we have tested the hypothesis that the synthetic steroid drug, methylprednisolone, acts primarily by interference with the activation of Hageman factor. This was evaluated by examining the effect of pretreatment with methylprednisolone on the response of two of these Hageman factor-activated systems, the plasma kinin and coagulation systems, to Escherichia coli septicemia in the baboon. An effect on these systems would suggest an indirect action of the drug in the treatment of gram-negative septicemia and not a variety of direct actions on diverse sites and processes.

Adult male baboons weighing 18 to 30 kg were used. Phencyclidine HCl, 0.1 mg/kg, was injected intramuscularly to sedate the animals for catheter insertions. No further sedation or anesthesia was used. All studies were performed with the animals semi-reclining in a restraining chair. Baboons were subjected to lethal Escherichia coli septicemic shock by injecting live organisms, with one group receiving pretreatment with 30 mg/kg of methylprednisolone and the other group serving as untreated control animals. There was an early development of disseminated intravascular coagulation and kinin activation in both groups, with progressive cardiovascular collapse and death in all animals. All animals, treated and untreated, died within 8 hours. The kinin precursor protein kininogen decreased to close to zero level. The difference between steroid-treated and nontreated groups was that plasma kallikrein levels declined significantly in the nontreated animals. Under the conditions of the study, no other effects of corticosteroid treatment of septic shock were observed.

KEY WORDS: baboon
E. coli shock
live E. coli organisms
intravascular coagulation
kinin
protein kininogen
kallikrein
steroid treatment
lethal septic shock
plasma proteins

HYPOGLYCEMIA IN LETHAL SEPTIC SHOCK IN SUBHUMAN PRIMATES

Hinshaw, L. B., B. Benjamin, J. J. Coalson, R. C. Elkins,
F. B. Taylor, Jr., J. T. Price, C. W. Smith, and L. J. Greenfield

Circ. Shock 2: 197-208, 1975

Recent research in this laboratory has documented progressively developing hypoglycemia in canine endotoxin shock. The purpose of the present study was to test these findings in a subhuman primate. Experiments were conducted on fasted baboons, anesthetized with sodium pentobarbital and infused with live Escherichia coli organisms (10^{10} organisms/kg). Six of seven baboons died within 26 hours with a mean survival time of 15 hours. Mean systemic pressures declined gradually after onset of organism infusion. An initial variable period of hypoerglycemia was observed in six animals followed by 4-15 hours of progressively developing hypoglycemia in all nonsurviving animals. Insulin values in arterial blood decreased markedly within 4 hours after E. coli infusion and remained low (10 to 20% of control) in all nonsurviving animals. Arterial blood lactate and serum potassium rose progressively in animals demonstrating the greatest degree of systemic hypotension, whereas pH remained relatively constant until preterminal periods.

Findings are in agreement with earlier studies reporting hyperglycemia and hypoinsulinemia, but reveal that the intermediate to terminal phase of shock is characterized by the progressive development of hypoglycemia and sustained hypoinsulinemia. A clear correlation is observed between levels of blood glucose and the pathophysiologic and lethal manifestations of experimental septic shock in the subhuman primate species.

KEY WORDS: baboon
septic shock
hypoglycemia
hypoinsulinemia
glucose
insulin
hyperglycemia
potassium
lactic acid

PHYSIOPATHOLOGIC RESPONSES OF THE RHESUS MONKEY TO LIVE ESCHERICHIA COLI

Hinshaw, L. B., B. Benjamin, L. T. Archer, B. Beller,
J. J. Coalson, and J. G. Hirsch

Surg. Gynec. Obstet. 142: 893-900, 1976

The present study was designed to develop an animal model applicable to the clinical patient in the investigation of the pathogenesis of septic shock. The model currently described is a lightly anesthetized, unrestrained monkey, carefully monitored during a 24-hour observation period. Varying doses of live Escherichia coli organisms were infused intravenously during a 30-minute period, and a variety of hemodynamic, respiratory and metabolic parameters were monitored. Doses of organisms varied between 7.6×10^9 and 3.0×10^{11} organisms per kilogram of body weight, and there was no obvious correlation between size of dose and survival time. Two of nine experimental monkeys survived the Escherichia coli, while times of death of the remaining monkeys varied between 3 and 27 hours. Two control monkeys, not administered organisms, survived the 24-hour period with minimal changes in all measured parameters. Results reveal two patterns in response to organism administration. These were early acute death, after 3 to 4 hours, and prolonged life, death after 20 to 27 hours. The acute response was characterized by marked systemic hypotension, hypoglycemia, hypoinsulinemia, increased lactate level, decreased pH or respiratory depression. The other type of response involved profound sustained hypotension with hypoglycemia and hypoinsulinemia in most monkeys and elevations in lactate, blood urea nitrogen, potassium, creatinine, serum glutamic-oxalacetic, lactic dehydrogenase and fractionated-lactic dehydrogenase levels. Depressions in respiration were not evident in the group which survived a longer period of time. Renal fibrin thrombi, prominent in baboons administered Escherichia coli, were absent in the rhesus monkey regardless of the size of the dose of organisms. The results of this study suggest the operation of a multifactorial mechanism in septic shock with interactions between hemodynamic and metabolic factors varying within the species.

KEY WORDS: rhesus monkey
E. coli organisms
septic shock
glucose
lactic acid
insulin
hypoglycemia
hypoinsulinemia
renal function

MONITORING RESUSCITATION OF PRIMATES FROM HEMORRHAGIC AND SEPTIC SHOCK

Trunkey, D., et al.

J. Amer. Coll. Emerg. Phys. 5: 249-252, 1976

See Section II on Hemorrhagic Shock, page 42.

II. HEMORRHAGIC SHOCK

SERUM INSULIN AND GROWTH HORMONE RESPONSE TO HEMORRHAGIC SHOCK

Cerchio, G. M., G. S. Moss, P. A. Popovich, E. Butler, and D. C. Siegel

Endocrinology 88: 138-143, 1971

Many metabolic abnormalities, including hyperglycemia and glucose intolerance, occur in hemorrhagic shock, which has been previously reported in dogs to be accompanied by elevations in plasma insulin levels. In this study, large primates (baboons) were subjected to hemorrhagic hypotension for 2 hours, during which time marked hyperglycemia occurred. Within 5 minutes of the onset of hemorrhage, insulin levels declined substantially in both fed and fasted animals and remained below pre-shock levels during the first hour of shock. During the second hour, insulin levels gradually rose, reaching levels slightly above base line values in approximately half the animals studied. Insulin response to intravenous tolbutamide was subnormal when administered after 1 hour of hypotension. Growth hormone levels remained suppressed in the majority of animals studied, and in the remaining animals changes in growth hormone levels did not correlate well with fluctuations in glucose concentration. These studies demonstrate that hemorrhagic shock in a primate species is associated with an immediate and significant decline in serum insulin concentration which may play an important role in the glucose intolerance of hemorrhagic states. Growth hormone levels during shock are not elevated, but remain suppressed in the majority of animals studied. The mechanism by which both insulin and growth hormone secretion are suppressed during hemorrhagic shock remains unclear.

KEY WORDS: baboon
hemorrhagic shock
insulin
glucose
growth hormones

THE METABOLISM OF FAT AND CARBOHYDRATE DURING HEMORRHAGIC SHOCK IN THE UNANESTHETIZED SUBHUMAN PRIMATE: CHANGES IN SERUM LEVELS OF FREE FATTY ACIDS, TOTAL LIPIDS, INSULIN, AND GLUCOSE

Coran, A. G., P. E. Cryer, D. L. Horwitz, and C. M. Herman

Surgery 71: 465-469, 1972

Previous work from this and other laboratories has shown that septic and hemorrhagic shock in the baboon are associated with hyperglycemia and hypoinsulinemia. Other studies in experimental animals and patients have emphasized the mobilization and possible elevation of serum free fatty acids during stress and shock. The relationship between carbohydrate changes and lipid mobilization is closely linked in the normal subject; changes in this relationship during shock may be critical in understanding changes in cellular metabolism and the possible toxic effects of elevations of certain lipid moieties. We have undertaken the study of the relationship between fat and carbohydrate in the awake baboon subjected to hemorrhagic hypotension.

Five adult baboons were subjected to hemorrhagic hypotension for a period of 3 1/2 hours, and another five baboons served as the control animals. The animals were studied in a specially designed chair while fully awake. During the period of hypotension, the cardiac output decreased significantly from 3.2±0.4 to 0.9±0.2 L/min, and the arterial lactate rose from 16.4±3.3 to 79.5±19.9 mg %. Thirty minutes after hemorrhage, the serum insulin had fallen from 19.0±0.1 to 7.6±0.8 μU/ml, and the glucose had risen to a peak of 252±20 mg %. Despite the development of hypoinsulinemia, no statistically significant acute change in the mean serum free fatty acid (FFA) concentration was demonstrable; however, after 3 1/2 hours the mean FFA level was 382% of baseline in the hypotensive group and not significantly raised in the control animals. Possible reasons why the early hemorrhagic hypoinsulinemia did not lead to the expected early elevation in the FFA's are discussed.

KEY WORDS: baboon
hemorrhagic shock
unanesthetized animal model
cardiac output
metabolism of fat, carbohydrate, free fatty acids, lipids, insulin and glucose

THE RELATIONSHIP OF CIRCULATING ENDOGENOUS ENDOTOXIN TO HEMORRHAGIC SHOCK IN THE BABOON

Herman, C. M., A. R. Kraft, K. R. Smith, E. J. Artnak, F. C. Chisholm, L. G. Dickson, E. E. McKee, Jr., L. D. Homer, and J. Levin

Ann. Surg. 179: 910-916, 1974

Experiments were carried out to test the hypothesis that during hemorrhagic shock endotoxin enters the circulation from ischemic bowel by way of the portal venous system and is then associated with irreversibility of the hemorrhagic shock state. After placement of sampling catheters in the portal vein, right atrium and aorta, 14 awake, restrained baboons were subjected to 1 hr of hemorrhagic shock at a mean arterial pressure (MAP) of 60 torr followed by a second hour at 40 torr MAP. Six animals were resuscitated with Ringers lactate and their shed blood; 8 were maintained hypotensive until death. Serial blood samples were analyzed for the presence of endotoxin. Endotoxemia was found infrequently, with no greater incidence ($p>0.6$) in portal venous samples than in systemic blood, so these data were pooled for further analysis. Furthermore, endotoxemia was no more frequent ($p>0.6$) late in shock than it was in early shock or during the baseline period. Autopsy showed no evidence of ischemic damage to the splanchnic viscera. It was concluded that spontaneous endogenous entotoxemia is not a common feature of hemorrhagic shock in baboons and is not related to the duration or degree of severity of hemorrhagic shock in this subhuman primate species.

KEY WORDS: baboon
hemorrhagic shock
endotoxin
splanchnic viscera
visceral pathology
endogenous endotoxin
endotoxin assay method

INSULIN RESPONSE TO HEMORRHAGIC SHOCK IN THE INTACT AND ADRENALECTOMIZED PRIMATE

Hiebert, J. M., Z. Celik, J. S. Soeldner, and R. H. Egdahl

Am. J. Surg. 125: 501-507, 1973

Glucose intolerance and initial hyperglycemia are well known responses to hemorrhagic shock. Blood levels of glucocorticoids, previously shown to rise in primates subjected to hemorrhagic shock, exert deleterious effects on glucose tolerance when insulin reserve is limited. In addition, the anticipated transient rise in serum insulin levels after glucose challenge is blunted in primates subjected to severe trauma and hemorrhagic shock. Furthermore, recent reports suggest that epinephrine infused in physiologic amounts in normal patients or monkeys inhibits glucose-stimulated insulin release. The rise in catecholamine blood levels observed during shock suggests a possible mechanism for the observed shock-induced suppression of insulin secretion after glucose administration.

The present study was undertaken in the primate to measure the influence of adrenal hormones on insulin secretion and glucose tolerance during hemorrhagic shock. For this measurement, a new method of estimating insulin secretion has been employed.

Fifteen rhesus monkeys were subjected to hemorrhagic shock. Five of these had intact adrenal glands and 10 had previously undergone bilateral adrenalectomy, five of them receiving hydrocortisone replacement. Portal blood flow and insulin secretory rates were measured during shock and after glucose administration. Five additional control monkeys underwent the same surgical and blood sampling protocol but were not subjected to hemorrhage. These studies suggest the following:

(1) Peripheral and portal blood insulin concentrations do not reflect insulin secretion rates during some stages of hemorrhagic shock.

(2) The inhibition of insulin secretion after either endogenously or exogenously induced hyperglycemia is probably due to adrenal medullary secretion.

(3) The acute secretion of insulin after glucose administration correlates better with glucose tolerance than with later peripheral blood insulin concentrations.

KEY WORDS: rhesus monkeys,
adrenalectomized
hemorrhagic shock
insulin response

SPECIES DIFFERENCES IN INSULIN SECRETORY RESPONSES DURING HEMORRHAGIC SHOCK

Hiebert, J. M., C. Kieler, J. S. Soeldner, and R. H. Egdahl

Surgery 79: 451-455, 1976

The hyperglycemic response to hemorrhagic shock appears to be a universal phenomenon. However, species differences have been reported regarding the insulin response to hyperglycemia during shock. In an effort to better define possible species differences in the insulin response during shock, insulin secretory rates before and after glucose were measured in dogs subjected to hemorrhagic shock and compared with monkeys undergoing the same procedure.

Insulin secretory rates (ISR) during intravenous glucose tolerance tests (IVGTT's) were measured in six dogs subjected to hemorrhagic shock and were compared to ISR's from five monkeys subjected to shock of comparable severity. ISR's also were measured in normotensive control dogs and monkeys subjected to the same blood sampling protocol. A sixfold increase in ISR occurred in shocked dogs after glucose loading; however, no ISR response occurred in monkeys subjected to hemorrhage. It is concluded that marked species differences exist in the insulin-glucose metabolic responses to shock. In addition, the dog would appear to be an inappropriate experimental animal as applied to trauma-insulin metabolism in man.

Despite the large differences in ISR between dogs and monkeys in shock no significant differences in glucose tolerance were observed. Thus it would appear that to varying degrees factors other than or in addition to insulin secretion control glucose metabolism during shock. Factors which diminish the effectiveness of insulin ("insulin resistance") may operate separately from the same or other factors which trigger and modulate insulin secretion. Indeed obesity, sepsis, and hypercorticosteroidism have been shown to alter glucose tolerance without diminishing insulin secretion. Our data appear to suggest that alterations in glucose metabolism during shock in the dog may be mediated principally through peripheral factors of "insulin resistance", whereas monkey glucose metabolism is influenced more by altered insulin secretion. These questions await further clarification. However, these studies do appear to indicate that the dog is a rather poor model for studies of insulin metabolism during shock as it applies to man.

KEY WORDS: rhesus monkey
hemorrhagic shock
insulin resistance
insulin response
in shock

EXTRAVASCULAR LUNG WATER FOLLOWING HEMORRHAGIC SHOCK IN THE BABOON: COMPARISON BETWEEN RESUSCITATION WITH RINGER'S LACTATE AND PLASMANATE

Holcroft, J. W., and D. D. Trunkey

Ann. Surg. 180: 408-417, 1974

Interstitial pulmonary edema is a common consequence of shock resuscitation. The type and amount of fluid used in resuscitation may be important determinants of the amount of edema formed. The pathophysiological basis for the "wet lungs" may be: 1) decreased serum oncotic pressure; 2) increased pulmonary capillary pressure; 3) increased pulmonary capillary permeability; or 4) a combination of these factors and others.

These experiments were designed to 1) measure the extravascular lung water accumulated after resuscitation from shock with colloids versus crystalloids and 2) determine if shock itself leads to increased pulmonary extravasation of colloids.

Baboons were subjected to deep hemorrhagic shock by using a membrane potential of -65 mv as an endpoint. They were then resuscitated with either Plasmanate plus their shed blood or Ringer's lactate plus their shed blood. As compared with their own preshock values, the Plasmanate-resuscitated animals accumulated more extravascular lung water than the Ringer's lactate-resuscitated animals. Another group of baboons resuscitated from deep shock demonstrated significant extravasation of albumin on postmortem analysis of lung composition. This increased tendency for extravasation of albumin after shock partially explains why resuscitation with Plasmanate gave no protection against the formation of pulmonary edema. The authors believe that Plasmanate, and probably other colloidal solutions, should be used sparingly in the initial treatment of deep hemorrhagic shock.

KEY WORDS: baboon
hemorrhagic shock
fluid therapy
shock lung

FURTHER ANALYSIS OF LUNG WATER IN BABOONS RESUSCITATED FROM HEMORRHAGIC SHOCK

Holcroft, J. W., D. D. Trunkey, and R. C. Lim

J. Surg. Res. 20: 291-297, 1976

The administration of human albumin, in moderate amounts, does no harm with respect to the formation of pulmonary edema in resuscitating baboons from deep, hemorrhagic shock. Neither does it offer any advantage over resuscitation with Ringer's lactate. No allergic reactions occurred in any of the animals exposed to Plasmanate and the finding of normal lung waters in the animals resuscitated with moderate amounts of Plasmanate would indicate further that baboons are not allergic to Plasmanate.

The administration of moderate amounts of dextran to resuscitate baboons from hemorrhagic shock may offer some advantage over RL-resuscitation. The dextran seems to alter the tendency for increased extravasation of albumin in the lungs after shock. Before advocating the clinical use of dextran, however, its mechanism of action must be established, particularly its effect on platelet function and the coagulation system. In addition, it may depress the reticuloendothelial system and increase the likelihood of secondary infection.

After deep hemorrhagic shock, albumin extravasates not only into the lungs in increased amounts, but also into the heart, brain, kidneys and liver. This extravasation would suggest that administering albumin after deep shock is unlikely to prevent edema formation in these other tissues as well.

KEY WORDS: baboon
hemorrhagic shock
treatment of shock
shock lung

role of therapies:
albumin
saline
dextran
Plasmanate

PULMONARY EXTRAVASATION OF ALBUMIN DURING AND AFTER HEMORRHAGIC SHOCK IN BABOONS

Holcroft, J. W., and D. D. Trunkey

J. Surg. Res. 18: 91-97, 1975

In this report, our initial studies on lung composition have been extended to include serial studies on 18 baboons during and up to 24 hours after shock. This report emphasizes the tendency for pulmonary extravasation of albumin after resuscitation from shock and the relation of this extravasation to the formation of pulmonary edema. The findings of these current studies support the conclusions of the original study, which recommended that acellular albumin-containing solutions be used sparingly or not at all in resuscitating patients from deep hemorrhagic shock.

The three main parts of the study involve: (1) measurement of the gravimetrically determined lung water, (2) measurement of the tendency for extravasation of albumin, and (3) the relation of the ELVW to the extravasation of albumin. The three principal conclusions are: First, resuscitation of baboons from deep hemorrhagic shock with crystalloid may lead to a transient increase in EVLW, but this excess EVLW is mobilized by the first day after shock. Second, albumin readily crosses out of the intravascular space into the pulmonary parenchyma after resuscitation from shock, but this tendency also returns to normal by the first day after shock. Third, EVLW* correlates positively with the tendency for extravasation.

*extravascular lung water (ELVW)

KEY WORDS: baboon
hemorrhagic shock
shock lung
pulmonary edema
therapy
albumin

EFFECTS OF STEROID PRETREATMENT ON DEVELOPMENT OF SHOCK LUNG: HEMODYNAMIC, RESPIRATORY AND MORPHOLOGIC STUDIES

Pingleton, W. W., et al.

Lab. Invest. 27: 445-456, 1972

See Section IA on Endotoxin Shock, page 17.

COMPARISON OF HEMODYNAMIC AND REGIONAL BLOOD FLOW CHANGES AT EQUIVALENT STAGES OF ENDOTOXIN AND HEMORRHAGIC SHOCK

Rutherford, R. B., et al.

J. Trauma 16: 886-897, 1976

See Section IA on Endotoxin Shock, page 21.

PULMONARY GAS EXCHANGE FOLLOWING HEMORRHAGIC SHOCK AND MASSIVE BLOOD TRANSFUSION IN THE BABOON

Tobey, R. E., C. J. Kopriva, L. D. Homer, R. T. Solis, L. G. Dickson, and C. M. Herman

Ann. Surg. 179: 316-321, 1974

There are no available controlled studies showing what effect, if any, infusion of stored blood has on arterial blood gases in an unanesthetized primate requiring blood because of hemorrhage. In order to evaluate the possible deleterious role of ACD blood upon pulmonary gas exchange, we designed an experiment to measure changes in arterial blood oxygen tensions after hemorrhagic shock and massive transfusion in an unanesthetized spontaneously breathing baboon.

Eleven juvenile baboons (Papeo doguera) weighing between 5.0 and 13.6 kg had a left thoracotomy and insertion of a pulmonary artery (PA) and left atrial (LA) catheters which were filled with heparin and secured subcutaneously. At least two weeks later the animals were anesthetized with Sernylan 1.1 mg/kg, the thoracic catheters exteriorized, two other catheters placed in the femoral artery (FA) and inferior vena cava (central venous pressure line) and a Yellow-Springs thermistor probe inserted either into the rectum or esophagus. The animals were placed in a restraining chair in a reclined position. Six hours after the administration of Sernylan the animals were awake and alert.

The five baboons in the experimental group were bled until mean systemic arterial pressure reached 60 mmHg. This pressure was maintained for one hour by withdrawal or infusion of the animal's own blood. Further hemorrhage lowered mean arterial pressure to 40-45 mmHg for an additional hour. No medications were given during the 2-hr shock period. Resuscitation was accomplished by transfusion of warmed, type-specific baboon blood which had been stored at 2-6°C for 16-21 days in 250 ml Fenwal plastic bags containing ACD solution. After mean systemic arterial pressure had been restored to baseline value and had stabilized 10 min, an isovolemic exchange transfusion was performed until a total of twice the calculated blood volume (144 ml/kg) had been infused.

The transfused blood was found to develop microaggregates similar in particle size and distribution to those in stored human blood. Arterial blood gas determinations obtained within 30 min after completion of the transfusion indicate no dysfunction in the capability of the lung to maintain P_aO_2, P_aCO_2 and pH after a period of severe shock and massive transfusion. No significant changes in mean systemic arterial, mean left atrial, mean pulmonary artery, or mean central venous pressures were noted. In particular, mean pulmonary arterial pressure was never elevated above 14 mmHg during transfusion. Light and electron microscopy findings did not demonstrate clear evidence of pulmonary microembolizations from the transfused blood.

The authors concluded that there is no incapacity of the lungs to maintain normal gas exchange immediately following shock and massive transfusion. From clinical and experimental data thus far published it is difficult to assess the role of transfusion following hemorrhagic shock in producing pulmonary dysfunction. Further studies are underway to determine whether hypoxemia is a late complication of shock and transfusion.

KEY WORDS: baboon
hemorrhagic shock
pulmonary function
therapy
blood transfusion effects
hypoxemia

MONITORING RESUSCITATION OF PRIMATES FROM HEMORRHAGIC AND SEPTIC SHOCK

Trunkey, D., J. Holcroft, and M. A. Carpenter

J. Amer. Coll. Emerg. Phys. 5: 249-252, 1976

Monitoring data in 16 primates subjected to septic or hemorrhagic shock and resuscitated with various solutions is presented. From a practical standpoint, central venous pressure and urine output appear to be the best indices to use in the emergency department for resuscitation of the shock victim. The sophisticated measurements such as cardiac output, thermodye volumes, pulmonary artery wedge pressure and oxygen consumption should be reserved for the individual with depressed cardiovascular reserves and who needs "fine tuning" of his volume status.

This discussion has assumed that the patient being resuscitated is capable of compensating for the cardiovascular insult. In some patients, however, such as the elderly person who may have antecedent heart disease, arteriosclerosis or pulmonary disease, these reserves may be impaired or absent. Therefore, they will be less tolerant of major insults. In fact, a minor insult such as a one unit blood loss may cause complete decompensation of the cardiovascular system. These patients will be more volume sensitive than the younger, healthy trauma victim and fine tuning of monitoring is required. In these instances the physician should strongly consider more sophisticated monitoring devices such as a Swan-Ganz catheter and obtaining PAW readings.

KEY WORDS: baboon
hemorrhagic shock
septic shock
therapy

CALCIUM FLUX DURING HEMORRHAGIC SHOCK IN BABOONS

Trunkey, D., J. Holcroft, and M. A. Carpenter

J. Trauma 16: 633-638, 1976

The purpose of this study was to measure changes in calcium and other electrolytes in the extracellular and intracellular spaces of skeletal muscle of primates following a control condition, deep hemorrhagic shock, resuscitation with Ringer's lactate and calcium-free Ringer's lactate resuscitation. We then related these changes to other physiologic measurements and their possible role in the pathophysiology of shock.

The animals were divided into two groups of 4 animals each. The first group was shocked and then resuscitated with a standard Ringer's lactate calcium-containing solution and measurements were made during the control, shock, and at two periods during resuscitation 2 1/2 hours and 24 hours following the shock insult. The second group was also shocked and resuscitated with a specially prepared Ringer's lactate solution containing no calcium. Measurements were at identical time periods to the first group.

This study represents the first reported in a series designed to define the role of calcium in the pathophysiology of shock. We have demonstrated a decrease in the concentration of extracellular calcium in hemorrhagic shock in baboons. This is aggravated by a calcium-free resuscitation. We also have demonstrated that there is an increase in extracellular concentration of magnesium during the shock period; however, this is minimized by a calcium-free resuscitation after 2 1/2 hours.

We conclude, at the present time, that calcium should be present in resuscitation fluids and that supplemental calcium should be given when massive transfusions are necessary.

KEY WORDS: baboon
hemorrhagic shock
role of calcium
therapy

EFFECTS OF HEMORRHAGE ON REGIONAL BLOOD FLOW DISTRIBUTION IN DOGS AND PRIMATES

Vatner, S. F.

J. Clin. Invest. 54: 225-235, 1974

The effects of hemorrhage on arterial pressure, blood flows, and resistances in the coronary, mesenteric, renal, and iliac beds of healthy, conscious dogs and intact, tranquilized baboons were studied.

Five baboons (Papio anubis) (24-26 kg), tranquilized with phencyclidine hydrochloride, 1 mg/kg, were studied. All operations were conducted under i.v. pentobarbital Na, 30 mg/kg. Doppler ultrasonic flow probes were placed around the left renal (5 baboons), mesenteric (3 babons), and iliac (3 baboons) arteries. In all animals blood was withdrawn from the catheter in the jugular vein until a sustained fall in mean arterial pressure of 20-30 mmHg was attained, while in three baboons hemorrhage was continued until a sustained fall of over 40 mmHg occurred. A moderate amount of hemorrhage, i.e., 20-30 mmHg reduction in mean arterial pressure, was chosen for an end point because it could be reproduced in all animals without signs of discomfort or restlessness.

Mild nonhypotensive hemorrhage (14±2 ml/kg) increased heart rate and mesenteric and iliac resistances slightly but significantly, and decreased renal resistance (-13±2%). Moderate hypotensive hemorrhage, 26±2 ml/kg, reduced mean arterial pressure (-23±2 mmHg) and blood flows to the mesenteric (-56±3%), iliac (-58±5%), and coronary (-39±4%) vascular beds, and increased heart rate (+89±9 beats/min) and resistances in the mesenteric (+73±15%), iliac (+102±19%), and coronary (+27±5%), beds. In contrast to the other beds, renal flow rose 11±6% above control and renal resistance fell 31±2% below control. Renal vasodilatation with hemorrhage was also observed in five baboons. The increases in mesenteric and iliac resistances were blocked almost completely by phentolamine, while the increase in coronary resistance was only partially blocked by phentolamine. The renal dilatation was not blocked by phentolamine, propranolol, atropine, or tripelennamine, but was prevented by indomethacin, suggesting that this dilatation was mediated by a prostaglandin-like compound.

Thus the peripheral vascular responses to hemorrhage involve intense vasoconstriction in the mesenteric and iliac beds. In the normal conscious dog and the intact, tranquilized primate, the renal bed does not share in the augmentation of total peripheral resistance with nonhypotensive and moderate hypotensive hemorrhage, but does with more severe hemorrhage. In fact, renal vasodilatation occurs with nonhypotensive or moderate hypotensive hemorrhage, which can be prevented by blockade of prostaglandin synthetase with indomethacin.

KEY WORDS: baboon
hemorrhagic shock
regional blood flow
α-adrenergic blockade
renal vascular resistance
flow probes
tranquilized animal preparation

III. OTHER PRIMATE REFERENCES OF SPECIAL INTEREST RELATED TO THE SHOCK FIELD

ACUTE CHANGES IN OXYHEMOGLOBIN AFFINITY: EFFECTS ON OXYGEN TRANSPORT AND UTILIZATION

Riggs, T. E., A. W. Shafer, and C. A. Guenter

J. Clin. Invest. 52: 2660-2663, 1973

It has been postulated that 2,3-diphosphoglycerate (DPG)-mediated changes in oxyhemoglobin affinity play an important role in oxygen delivery; however, the effect of an acute increase in affinity without changing red cell mass has not been systematically evaluated. This study was designed to measure changes in oxygen transport and oxygen consumption produced by an acute increase in oxyhemoglobin affinity caused by an autologous exchange transfusion using DPG-depleted stored blood.

From each of ten 5-kg rhesus monkeys, 100 ml of blood was taken on the 1st and 3rd week of the study and each stored in 25 ml of acid-citrate-dextrose storage solution. At the beginning of the 5th week, all animals were anesthetized with sodium pentobarbital, 25 mg/kg body weight, and the trachea intubated. Studies were performed during a control period. This was followed by a 200 ml exchange transfusion in 25-ml increments over a 20 min period with autologous blood that previously had been warmed to body temperature. Thirty min after the transfusion repeat hemodynamic studies were obtained. A flow-directed polyethylene (PE 90) catheter was placed in the main pulmonary artery and its position confirmed fluoroscopically and by pulse contours. A Teflon catheter was placed in the femoral artery. Cardiac output was measured during the expired gas collection by the indicator-dilution technique, as previously described, before the blood samples for gases and saturations were withdrawn.

Expired gases were collected in a recording underwater seal spirometer to permit measurement of oxygen consumption. Simultaneous arterial and mixed venous (pulmonary arterial) blood samples were obtained. The expired gases and blood were analyzed with an Instrumentation Laboratory blood gas analyzer and pH electrode. Hemoglobin concentration and oxygen saturation were measured with an Instrumentation Laboratory Co-oximeter. Base excess was determined using the Severinghaus blood gas calculator. Hematocrits and mean corpuscular hemoglobin concentrations were not measured.

Hemoglobin's affinity for oxygen, expressed as P_{50} (the PO_2 at which hemoglobin is 50% saturated), was measured by reproducing the oxyhemoglobin dissociation curve, using the mixing technique as previously described. The oxyhemoglobin dissociation curve shifted to the left (P_{50} changed from 33.9 to 27.2 mmHg), as mean red cell DPG decreased from 28.6 to 12.7 μmol/g of hemoglobin. No significant change was noted in pH, PCO_2, base deficit, arterial or venous percent saturation, of hemoglobin, cardiac output, or oxygen consumption. However, a fall in mixed venous PO_2 from 35.3 to 27.9 mmHg occurred.

Thus, an acute shift of the oxyhemoglobin curve to the left was accompanied by a significant decrease in the mixed venous PO_2 without evidence of acidosis, decreased oxygen consumption, or a compensatory increase in cardiac output.

KEY WORDS: rhesus monkey oxyhemoglobin affinity oxygen transport stored blood

INHIBITION OF INSULIN SECRETION BY INFUSED EPINEPHRINE IN RHESUS MONKEYS

Kris, A. O., R. E. Miller, F. E. Wherry, and J. W. Mason

Endocrinology 78: 87-97, 1966

Metabolic antagonism between epinephrine and insulin, especially in the regulation of blood sugar, is well known. Less attention has been paid to possible actions of these hormones in regulating each other. The present in vivo experiments on the inhibition of insulin secretion by epinephrine were undertaken when preliminary studies of the effects of infused epinephrine on several hormones revealed a striking rise in plasma glucose without a concomitant rise in plasma insulin.

The effect of infused *l*-epinephrine bitartrate on plasma insulin levels has been studied in the fasted, normal, waking rhesus monkey, with chronically implanted venous catheters. Male rhesus monkeys, weighing 3.5-4.5 kg, were used in all experiments. Animals were maintained in restraining chairs, housed in sound-resistant cubicles and permitted to recover from surgery and adapt to the chair for at least 2 weeks prior to the experiment. The catheters were extended through the top of the cubicles so that infusions and blood-sampling could be performed without handling or confronting the animal.

Experiments were performed at the same time each day, 21 hr after feeding. Each animal was used in a series of experiments with an interval of at least 3 days between experiments. As a preliminary to other experiments, increased plasma insulin levels were demonstrated in each animal when 9 g of glucose was infused over 15 min. No animal was found unresponsive.

It was demonstrated that sharp rises in peripheral plasma glucose levels during infusion were not accompanied by rises in plasma insulin levels but that these did rise rapidly following the end of infusion in the majority of cases. The same phenomenon was seen when large amounts of intravenous glucose were given during epinephrine infusion. Further experiments showed that portal vein plasma insulin levels were also suppressed in the same way by epinephrine. No effect of epinephrine on plasma insulin levels was seen when epinephrine was added to plasma in vitro, and no effect of infused epinephrine on disappearance of injected insulin was found. These results were interpreted to mean that infused epinephrine inhibits secretion of insulin. Further findings were presented to reject the hypothesis that this effect of epinephrine is a consequence of its psychological (anxiety-like) effects, through sensations it may arouse. A series of experiments on a single animal, with carotid artery infusion of epinephrine, suggest that the brain is not the site of action.

KEY WORDS: rhesus monkey
insulin secretion
epinephrine infusion
plasma glucose
plasma insulin

PANCREATIC BETA CELL REPLICATION INDUCED BY GLUCOCORTICOIDS IN SUBHUMAN PRIMATES

Like, A. A., and W. L. Chick

Am. J. Path. 75: 329-348, 1974

For the past several years, attention has been directed to the beta cell as a primary site of pathology in genetic human diabetes mellitus. It is clearly apparent that the course and outcome of the disease may be a function of the ability of the animal to produce new beta cells during periods of hyperglycemia.

Pancreatic islets were studied by means of light microscopy, autoradiography and electron microscopy in untreated Macaca cyclopis monkeys and after the administration of large quantities of adrenal glucocorticoids. Mild hyperglycemia and profound elevations of serum immunoreactive insulin were induced by glucocorticoid injections of 1-3 weeks duration, with a gradual return to pretreatment levels within 2 months after cessation of treatment. Morphologic alterations included degranulation and hyperplasia of pancreatic beta cells. These were noted in association with increased numbers of labeled islet cells after the administration of ^{3}H-thymidine and beta cells undergoing mitotic division, and could be correlated directly with the magnitude of serum insulin elevation. Evidence of acinar-islet or duct-islet cell transformation was absent. Beta cell regranulation and the twofold increase in extractable pancreatic insulin which followed the cessation of injections demonstrated the survival and functional integrity of the newly formed beta cells.

KEY WORDS: Macaca cyclopis monkey
pancreatic cells
glucocorticoids
hyperglycemia

NEUROGENIC INFLUENCE ON PULMONARY COMPLIANCE

Beckman, D. L., J. W. Bean, and D. R. Baslock

J. Trauma 14: 111-115, 1974

Experimental studies have shown that mechanical trauma to the head and severe CNS dysfunction frequently result in pulmonary complications in these conditions. Pretreatment with various sympatholytic, anti-epinephrine, and general anesthetic agents prevents these pulmonary changes, suggestive of an important neuroendocrine influence on pulmonary surfactants and compliance in head injury. Such changes occurred even in the absence of any gross lung damage as indicated by normal lung weights. The studies reported herein were performed to determine what effect direct sympathetic stimulation by way of the stellate ganglion might have on the cyclical transpulmonary pressure, and possibly on the alveolar surfactants.

The present experiments were carried out as a further investigation of the possible involvement of the sympathetics in the regulation of alveolar surfactants and lung compliance. Young adult squirrel monkeys (500-700 g) were anesthetized with ketamine (Vetalar, 20 mg/kg, i.m.). Stimulation of the pulmonary sympathetics by an electrode attached to the stellate ganglion in five monkeys, anesthetized with ketamine, resulted in an abnormally high minimum surface tension of the lung wash, suggestive of an alteration in the alveolar surfactants. This interpretation was supported by findings from an additional 11 monkeys that stellate ganglion stimulation caused a statistically significant 20% increase in the cyclical transpulmonary pressure without alterating gross lung appearance or lung weight/body weight ratio from that of sham-operated controls.

KEY WORDS: squirrel monkey
neurogenic influence
brain, lung pathology
stellate stimulation

EFFECTS OF GLUCOSE, INSULIN AND POTASSIUM INFUSION ON TISSUE METABOLIC CHANGES WITHIN FIRST HOUR OF MYOCARDIAL INFARCTION IN THE BABOON

Opie, L. H., K. Bruyneel, and P. Owen

Circulation 52: 49-57, 1975

An important concept, recently emphasized in the management of acute myocardial infarction, is that the severity of heart tissue damage might be modified by various procedures including metabolic manipulation. Although experiments on dogs have suggested that infusions of glucose, insulin and potassium (GIK) might exert a beneficial influence on the effects of coronary artery ligation by decreasing the extent of mitochondrial damage and the infarct size, yet many more experimental details are required before GIK can be recommended for general clinical use.

The effects of infusions of glucose, insulin and potassium (GIK) on the heart tissue metabolic changes found in adult baboons 60 minutes after coronary artery ligation were studied. Biopsies taken from 11 baboons without coronary artery ligation gave control values. A second group of 46 baboons had coronary artery ligation A third group of 17 baboons received an infusion of KCl after coronary artery ligation. A fourth group of 26 baboons received infusions of GIK. Coronary artery ligation resulted in the expected fall of ATP, creatine phosphate, glycogen, tissue (K^+/Na^+) ratio, and tissue pH, and rise of inorganic phosphate, lactate, lactate/pyruvate ratio and α-glycerophosphate in the infarction zones. Compared with ligation, additional infusions of GIK approximately doubled the contents of creatinine phosphate and glycogen in the infarct zones, increased the content of ATP in the central infarct zone, and decreased the content of inorganic phosphate in the peripheral infarct zone. Other GIK effects were that the tissue (K^+/Na^+) ratio rose in the peripheral infarct zone, and the content of both glycogen and lactate rose in the peri-infarct and non-ischemic zones; the pH of tissue homogenates did not decrease. KCl infusions had few effects compared with the ligation group. GIK infusions exerted a beneficial effect when compared with infusions of KCl in that tissue creatine phosphate rose in the peripheral infarct and non-ischemic zones; and the lactate/pyruvate ratio fell in the infarct zone. It is proposed that GIK counteracted early tissue metabolic deterioration in the infarcting baboon heart.

KEY WORDS: baboon
heart failure
glucose, insulin, and potassium (GIK)
therapy
myocardial infarction
lactate

DEIODINATION OF l-THYROXINE IN VITRO BY PERIPHERAL LEUKOCYTES FROM RHESUS MONKEYS WITH BACTERIAL SEPSIS

Derubertis, F. R.

J. Lab. Clin. Med. 83: 902-910, 1974

Accelerated host metabolism of l-thyroxine (T_4) has been observed during acute bacterial pneumonia in man and during bacterial sepsis in the rhesus monkey. These illnesses are characterized by significant increases in the number of circulating leukocytes. Since leukocytes stimulated to phagocytize in vitro accumulate and deiodinate T_4 more rapidly than resting cells, it seemed possible that the enhanced metabolism of T_4 accompanying some acute bacterial infections might, at least in part, be attributable to increased deiodination of T4 by activated leukocytes of the infected host. There is evidence to suggest that in vitro deiodination of T4 by leukocytes from infected monkeys may be increased, although this possibility was not examined in detail. Accordingly, in the present study, the degradation of T4 by peripheral leukocytes from monkeys with Salmonella typhimurium sepsis was assessed in vitro.

The deiodination of l-thyroxine (T_4) in vitro by peripheral leukocytes isolated from healthy rhesus monkeys was compared to that of leukocytes from monkeys with acute Salmonella typhimurium sepsis, an infection associated with accelerated metabolism of T_4 in vivo. Deiodination of T_4 by leukocytes from septic monkey donors was significantly enhanced, with inorganic iodide identified chromatographically as the predominant product of T_4 degradation. Induction of phagocytosis in vitro potentiated the T_4 deiodinating activity of leukocytes from both control and infected monkeys. However, the proportion of added T_4 degraded by leukocytes from septic donors following stimulation of phagocytosis in vitro was nearly twice that of cells from controls. Although mixed populations of isolated leukocytes (predominantly neutrophils and lymphocytes) were studied, the metabolism of T4 in vitro was almost exclusively an action of the neutrophil. By contrast with the enhanced T_4 deiodinating activity of neutrophils from septic hosts, the rate of ^{14}C-1-glucose oxidation in vitro by these cells was not detectably different from that of neutrophils from control monkeys, when assessed basally or after induction of phagocytosis. The data suggest that deiodination of T_4 by host neutrophils might contribute to the acceleration of T_4 metabolism observed in vivo during some acute infections. The quantitative importance of neutrophil metabolism of T_4 in vivo, the mechanisms mediating enhanced hormonal degradation by these cells, and the extent to which iodide released from T_4 is utilized in the myeloperoxidase-H_2O_2-halide antimicrobial system as part of a host-defense system against invasive bacteria remain uncertain.

KEY WORDS: rhesus monkey
sepsis (Salmonella)
leukocytes
neutrophils
thyroxine

PHYSIOLOGIC EFFECTS OF NORMAL- OR LOW-OXYGEN-AFFINITY RED CELLS IN HYPOXIC BABOONS

Spector, J. I., C. G. Zaroulis, L. E. Pivacek,
C. P. Emerson, and C. R. Valeri

Am. J. Physiol. 232: H79-H84, 1977

Baboons were bled one-third their red cell mass and were given homologous transfusions of red blood cells to restore the red cell volume. One group of baboons received red blood cells with a normal 2,3-diphosphoglycerate (2,3-DPG) level and normal affinity for oxygen, and in this group the 2,3-DPG level after transfusion was normal. The other group received red blood cells with a 160% of normal 2,3-DPG level and decreased affinity for oxygen, and in this group the 2,3-DPG level after transfusion was 125% of normal. In both groups of baboons, the inspired oxygen concentration was lowered and arterial PO_2 tension was maintained at 55-60 mmHg for 2 hours after transfusion. During the hypoxic state, systemic oxygen extraction was similar in the two groups, whereas oxygen saturation was lower in the high 2,3-DPG group than in the control animals. Cardiac output was significantly reduced 30 minutes after the arterial PO_2 was restored to normal. These data indicate that red blood cells with decreased affinity for oxygen maintained satisfactory oxygen delivery to tissue during hypoxia.

KEY WORDS: baboon
cardiac output
oxygen consumption
blood gases
in vivo and *in vitro* P_{50} values
2,3-DPG levels
arterial hypoxemia

PORTAL AND PERIPHERAL VEIN INSULIN RESPONSES TO INTRAVENOUS GLUCOSE IN THE RHESUS MONKEY

Rayfield, E. J., R. T. Faulkner, and W. Czajkowski

J. Lab. Clin. Med. 87: 919-924, 1976

Most physiological studies of insulin secretion have measured only peripheral blood insulin concentrations with the assumption that changes in such peripheral levels would mirror changes in pancreatic insulin secretion. However, since almost all pancreatic vein insulin must traverse the liver (via the portal vein) before entrance into the systemic circulation, and insulinases are present the liver, the liver is an important regulator of peripheral insulin concentrations. The purpose of the present study was to assess concomitant portal and peripheral vein insulin responses to an intravenous glucose load as well as to ascertain whether a biphasic insulin secretory response occurs in normal rhesus monkeys.

Catheterization of the portal vein and bilateral femoral veins were performed under general anesthesia in 6 healthy male rhesus monkeys. Four days later, sequential, simultaneous peripheral and portal plasma samples were obtained for glucose and immunoreactive insulin determinations before and after administration of 0.5 gm of glucose/kg (over a 1-minute period) via the opposite peripheral catheter. Two phases of insulin secretion were noted in both portal and peripheral plasma samples. An immediate early-phase insulin response was noted with a peak response at 1 minute followed by a rapid decline to a nadir at 5 minutes. A second phase of insulin secretion was evident with a peak response at 10 minutes and a subsequent decline to basal levels by 60 minutes. Simultaneous portal vein and peripheral vein glucose concentrations were not significantly different from each other by paired analysis. Thus, in the rhesus monkey peripheral insulin concentrations following intravenous glucose exhibit a biphasic response closely paralleling pancreatic insulin secretion.

KEY WORDS: rhesus monkey, insulin, glucose, liver

EFFECTS OF DECREASING ARTERIAL BLOOD PRESSURE ON CEREBRAL BLOOD FLOW IN THE BABOON: INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM

Fitch, W., E. T. MacKenzie, and A. M. Harper

Circ. Res. 37: 550-557, 1975

Constancy of cerebral blood flow is maintained in the face of moderate variations in systemic arterial blood pressure, but the nature of this phenomenon is a matter of some debate. One view is that this mechanism is intrinsic. According to this view, cerebral blood flow is regulated by tissue metabolites or by a myogenic, Bayliss reflex. If either of these hypotheses is correct, then the blood pressure-flow relationship is a result of autoregulation. The other major view is that the characteristic blood pressure-flow relationship of the cerebral circulation is controlled or modified by the extrinsic innervation of the cerebral vasculature--the neurogenic hypothesis.

The present study was undertaken to investigate the effects of surgical (acute and chronic) cervical sympathectomy and of α-receptor blockade (phenoxybenzamine) on the cerebral pressure-flow relationship existing during hypotension induced by hemorrhage.

The influence of the sympathetic nervous system on the cerebral circulatory response to graded reductions in mean arterial blood pressure was studied in anesthetized baboons. Cerebral blood flow was measured by the ^{133}Xe clearance method, and arterial blood pressure was decreased by controlled hemorrhage. In normal baboons, the constancy of cerebral blood flow was maintained until mean arterial blood pressure was approximately 65% of the base-line value; thereafter, cerebral blood flow decreased when arterial blood pressure was reduced. Superior cervical sympathectomy of 2-3 weeks duration did not affect the normal response. In contrast, both acute surgical sympathectomy (cervical trunk division) and α-receptor blockade (1.5 mg/kg of phenoxybenzamine) enhanced the maintenance of cerebral blood flow in the face of hemorrhagic hypotension in that cerebral blood flow did not decrease until mean arterial blood pressure was approximately 35% of the base-line value. The results indicate that the sympathetic nervous system is not involved in the maintenance of cerebral blood flow in the face of a fall in arterial blood pressure. Indeed, the implication is that the sympathicoadrenal discharge accompanying hemorrhagic hypotension is detrimental to, rather than responsible for, cerebral autoregulation.

KEY WORDS: baboon
blood pressure
hypotension
brain perfusion
sympathetic nervous system
cerebral blood flow

USE OF BABOONS IN STUDIES OF ACUTE MYOCARDIAL INFARCTION AND EFFECTS OF GLUCOSE, INSULIN AND POTASSIUM (GIK)

Bruyneel, K., and L. H. Opie

Acta Med. Scand. (Suppl. 587): 65-69, 1976

By the use of labeled microspheres, we found that the flow in the centre of the infarct (area 1) was 5-10% of the preligation flow; in area 2 (peripheral infarct zone) flow was 20-30%; and in area 3 (a narrow band 1-2 mm in width and an apparently normal non-cyanotic area surrounding the infarct) flow was about 70% in non-fibrillating baboons and normal in fibrillating baboons. In 26 baboons the effects of glucose, insulin and potassium (GIK) infusions were studied. The infusion was started at 3 minutes after coronary artery ligation at a rate of 0.2 ml/kg/min. Twelve baboons received 100 g/L glucose with 40 mEq KCl and 40 U insulin; 14 other baboons received 200 or 500 g/L glucose and 60 mEq KCl and 60 U insulin; these two rates of provision of GIK gave similar results which were combined. The insulin was NUSO (Wellcome) and glucagon low. Biopsies were taken from the heart 60 minutes after the coronary artery ligation and compared with 12 baboons who had a coronary ligation and an infusion of 0.45 g/L NaCl or no infusion.

Besides tissue metabolic changes, the GIK infusion reduced circulating FFA by about half, and increased diuresis. The only significant effect of GIK infusion on epicardial ST-segment changes consisted of prevention of the full development of ST-depression in area 3 (peri-infarct zone).

We conclude that GIK had a beneficial effect and counteracted early tissue metabolic deterioration in the infarcting baboon heart. However, our results do not provide a simple answer about the active principle in GIK nor about the complex and probably multilevel effect of glucose, insulin and potassium on acute myocardial infarction.

KEY WORDS: baboon
myocardial infarction
heart dysfunction
GIK therapy

CARDIOVASCULAR AND RENAL FUNCTIONS IN NORMAL RHESUS MACAQUES

Liu, C. T.

Am. J. Vet. Res. 37: 969-974, 1976

Techniques on measurements of cardiovascular and renal functions in conscious rhesus macaques (Macaca mulatta) are described, and normal base line values are presented. The determinations included blood pressure, cardiac dynamics, total peripheral resistance, renal metabolism, renal concentrating capacity, acid-base balance, and renal handling of electrolytes.

The rhesus macaques were divided randomly into four groups:

Group	No.	Distinctive measurements
I	40	Tubular maximal reabsorption of glucose, clearance of p-aminohippurate, and electrolyte excretion
II	27	Cardivascular, renal hemodynamics, and metabolism
III	31	Tubular maximal secretion of p-amino-hippurate and electrolyte excretion
IV	5	Renal hemodyanmics

KEY WORDS: rhesus monkeys
physiological functions, values of
cardiac output
blood pressure
total peripheral resistance
renal function

EXPERIMENTAL CEREBRAL HEMODYNAMICS: VASOMOTOR TONE, CRITICAL CLOSING PRESSURE, AND VASCULAR BED RESISTANCE

Dewey, R. C., H. P. Pieper, and W. E. Hunt

J. Neurosurg. 41: 597-606, 1974

The response of the cerebral circulation to changes in mean arterial pressure is well known. Flow is maintained constant at pressures between 50 and 150 mmHg by adjustments of vasomotor tone; this is due to autoregulation. It has long been presumed that the vasomotor responses maintain constant flow by adjusting the caliber of the resistance vessel. No previous work has demonstrated the mechanism whereby changes in vasomotor tone produce changes in cerebral blood flow (CBF).

Application of Burton's concept of the critical closing pressure to experimental data on brain-blood flow in the monkey suggests that perfusion pressure, not vascular bed resistance, is the primary variable affecting cerebral blood flow. Perfusion pressure for the cerebral circulation is the mean arterial pressure minus the critical closing pressure (MAP - CCP). Vasomotor tone and intracranial pressure are the major determinants of the critical closing pressure. Changes in either of these variables, therefore, affect perfusion pressure and flow. Data on brain-blood flow at fixed vasomotor tone obtained over wide pressure ranges show little change in vascular bed resistance despite significant changes in flow. The diameter of resistance vessels probably does not change significantly throughout the normal physiological range of cerebral blood flow. The limits of the critical closing pressure in the anesthetized monkey are from 10 to 95 mmHg. Using these limits, and beginning with the average values for MAP and CCP in 11 awake monkeys breathing room air, the authors present theoretical flow curves in response to changes in intracranial pressure and mean arterial pressure that closely approximate the data reported in man.

KEY WORDS: rhesus monkey
cerebral hemodynamics
critical closing pressure
"driving pressure"
vasomotor tone

RETICULOENDOTHELIAL FUNCTION: DETERMINANT FOR SURVIVAL FOLLOWING HEPATIC ISCHEMIA IN THE BABOON

Olcay, I., K. Holper, A. Kitahama, R. H. Miller, T. Drapanas, R. A. Trejo, and N. R. Di Luzio

Surgery 76: 643-653, 1974

The influence of hepatic ischemia on reticuloendothelial (RE) function and on the development of systemic endotoxemia was evaluated and related to subsequent mortality patterns of Papio papio baboons. Of baboons undergoing 60 minutes of complete hepatic vascular occlusion, 60% manifested endotoxemia in both portal venous and femoral arterial plasma. All animals undergoing 90 minutes of hepatic ischemia developed systemic endotoxemia. Blood samples obtained from sham-operated and experimental animals prior to occlusion were endotoxin negative. The degree and persistence of endotoxemia did not appear to correlate with the ultimate fate of the animal. In contrast, RE dysfunction, as reflected by the impairment in the clearance of the ^{131}I-triolein RE test-lipid emulsion correlated with ultimate mortality patterns. Baboons which developed phagocytic depression 24 hours after hepatic insult ultimately died, while those which manifested minor modifications of RE function survived. These studies reveal that RE dysfunction may be contributory to fatal outcome in shock due to hepatic ischemia.

KEY WORDS: baboon
liver ischemia
reticuloendothelial function
endotoxemia
limulus test for endotoxin

EFFECTS OF HYPOTENSION ON RHESUS MONKEYS

Gamache, F. W., Jr., and R. E. Myers

Arch. Neurol. 32: 374-380, 1975

During surgery on humans, the practice of lowering the arterial blood pressure is currently in wide use for the prevention or control of bleeding. Thus, an urgent need exists for a better knowledge of the body's tolerances to blood pressure lowering of different degrees and for different durations. The present study utilized a rhesus monkey model where the blood pressure alone was varied while the blood composition was well maintained to study the specific physiological and neuropathological effects of hypotension.

Twenty-one late-juvenile rhesus monkeys were rendered profoundly hypotensive for 0-, 15-, or 30-minute periods by means of infusion of trimethaphan camsylate. Blood pressure was then restored to prehypotensive levels with phenylephrine infusions. Respiratory gas tensions and pH of arterial blood were maintained within their normal limits throughout experimental and recovery periods.

Animals either recovered and showed no sequelae or died 12 to 48 hours later of cardiorespiratory difficulties, often accompanied by brain swelling. Brain injury and death occurred in 64% of cases when arterial blood pressure was maintained at 25 mmHg for up to 30 minutes. Multifocal myoclonus, depressed electroencephalographic activity, rises in cisternal cerebrospinal (CSF) pressures, respiratory depression, and characteristic changes in serum and cisternal CSF glucose followed episodes of controlled hypotension. Hypoxia and acidosis occurring during insult or recovery periods rather than hypotension itself probably account for neuropathological sequelae described by others.

KEY WORDS: rhesus monkey
hypotension
brain injury
CSF glucose changes

CONTROL OF HEPATIC GLYCOGEN METABOLISM IN THE RHESUS MONKEY: EFFECT OF GLUCOSE, INSULIN, AND GLUCAGON ADMINISTRATION

Curnow, R. T., E. J. Rayfield, D. T. George, T. V. Zenser, and F. De Rubertis

Am. J. Physiol. 228: 80-87, 1975

The effects of intravenous glucose, insulin and glucagon administration on the hepatic glycogen synthase and glycogen phosphorylase systems were assessed in the anesthetized rhesus monkey. Results were correlated with measurements of hepatic cyclic AMP (cAMP) concentrations and plasma glucose, insulin, and glucagon concentrations. Both glucose and insulin administration promoted significant inactivation of phosphorylase by 1 min, which was followed by more gradual activation of synthase. Neither glucose nor insulin caused significant changes in hepatic cAMP. Marked hyperglucagonemia resulting from insulin-induced hypoglycemia did not cause increases in hepatic cAMP, suggesting that the elevated insulin levels possibly inhibited glucagon action on the hepatic adenylate cyclase-cAMP system. Glucagon administration caused large increases in hepatic cAMP and activation of phosphorylase within 1 min, followed by more gradual inactivation of synthase when it had been previously activated by glucose. Concomitant glucose infusion, with resulting increased plasma insulin concentrations, markedly diminished the duration of hepatic cAMP elevations following glucagon administration, again suggesting an insulin inhibition of glucagon action on the hepatic adenylate cyclase-cAMP system.

KEY WORDS: rhesus monkey
hepatic cAMP
plasma glucose
hypoglycemia
plasma insulin
plasma glucagon
hyperglycemia

CORONARY ARTERY LIGATION IN THE BABOON AS A MODEL OF ACUTE MYOCARDIAL INFARCTION: FAILURE OF GLUCOSE, POTASSIUM, AND INSULIN TREATMENT TO INFLUENCE MITOCHONDRIAL METABOLISM AND ENERGETICS

Lochner, A., L. H. Opie, A. Gray, P. Owen, K. Bruyneel, J. J. Van der Walt, J. C. N. Kotze, and W. Gevers

Recent Adv. Stud. Cardiac Struct. Metab. 3: 685-691, 1973

Considerable interest has recently been shown in the possibility that the outcome of experimental coronary artery occlusion could be modified by metabolic manipulation. According to the "glucose hypothesis", increased provision of glucose to the infarcting myocardium could act beneficially by (1) promoting the anaerobic glycolysis, (2) decreasing potassium loss, (3) maintaining the cell action potential, and (4) depressing high circulating FFA levels. Because of the failure of insulin secretion and insulin resistance which is sometimes found in patients with acute myocardial infarction, it would be logical to add insulin to a glucose infusion. The combination of glucose and insulin decreases circulating potassium, which in turn may predispose to arrhythmias. Hence the addition of potassium to this regime might seem desirable. A potassium, glucose, insulin (KGI) regime has been popularized, chiefly with the aim of preventing K^+ loss from the ischemic tissue.

Acute regional myocardial ischemia was produced in the baboon heart by ligation of the anterior descending coronary artery or branches of the circumflex artery, or both. The cyanosed infarcting area was well demarcated on the surface by a sharp edge and by ST elevation on the epicardial ECG. The average size of the infarct was 10-12% of the whole heart. One hour after ligation, tissue biopsies were taken from four zones: (1) the center of the infarcting area, where maximal ST elevation was obtained on the epicardial ECG; (2) periphery of the infarcting area, where ST elevation was less marked; (3) apparently normal tissue immediately adjacent to the infarction where there was usually ST-segment depression; and (4) left ventricular tissue far from the infarcting area, where the ST-segment was usually isoelectric. Phosphorylation to oxidation ratios, determined manometrically and polarographically on isolated mitochondria, were significantly depressed in the infarcting myocardium, as was the respiratory control index. Oxygen uptake by the isolated mitochondria was similar in all areas studied, indicating a specific defect in phosphorylation of mitochondria derived from infarcting tissue. Drill and slice biopsies taken at the end of the experimental period showed severe depletion of ATP and phosphocreatine in the infarcting myocardium. The whole tissue K^+ content only decreased by about 10% in the infarcting myocardium. The plasma K^+ fell during the experimental period. To eliminate any effect this fall could have on mitochondria metabolism, an infusion of KCl was given to some baboons. However, mitochondria from infarcting areas of KCl-infused baboons showed a similar depression in oxidative phosphorylation. Potassium-glucose-insulin treatment had no effect on the following parameters: mitochondrial P/O ratio, tissue ATO and phosphocreatine, tissue lactate, epicardial ST eleva-

tion, and apparent size of the infarction. Failure of potassium-glucose-insulin to modify the outcome of coronary artery ligation could be explained by the low rate of collateral flow to the infarcting myocardium in the baboon. However, similar results have been obtained in the dog.

KEY WORDS: baboon
GIK therapy
myocardial dysfunction
mitochondrial function

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